Libby - toxicity

Fw: Region 8 comments on Libby Asbestos File

Carol Campbell to: Judy Hansen 03/24/2011 07:36 AM

Please print
Deborah McKean

----- Original Message -----
From: Deborah McKean
Sent: 03/23/2011 08:44 PM EDT
To: Carol Campbell
Subject: Fw: Region 8 comments on Libby Asbestos File

Here are the R8 comments on the cancer IUR.
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Susan Griffin

----- Original Message -----
From: Susan Griffin
Sent: 03/21/2011 10:31 AM MDT
To: David Berry; Wendy OBrien; Bob Benson
Cc: Deborah McKean
Subject: Region 8 comments on Libby Asbestos File

Hi All,

Attached are the Region 8 comments on the Libby Asbestos Toxicological Review and External Peer Review Questions. I want to thank all three of you for your REALLY thorough and knowledgeable comments. Wendy, you are the gold standard in writing easy to follow and easy to incorporate comments! Needless to say, I couldn't have done it without you. I may need to call on your expertise again if the chemical file manager wants to follow up.

Thanks again,
Susan


Libby Asbestos Reg 8 comments.docx


Libby Asbestos charge questions Reg 8.docx

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17 March 2011

MEMORANDUM

SUBJECT: Comments on Toxicological Review Libby Amphibole Asbestos

FROM: Susan Griffin, PhD DABT, David Berry PhD, Wendy O'Brien, PhD and Robert Benson PhD
Region 8 Toxicologists

TO: Karen Hammerstrom, PhD
IRIS Program

Thank you for the opportunity to review the Toxicological Review document on Libby Amphibole Asbestos. As you can see, the Region 8 Toxicologists had extensive comments on the document and derivation of the Inhalation Unit Risk (IUR) for Libby Asbestos. The most serious concerns dealt with the exclusion of more recently published data from the mesothelioma evaluation, dose reconstruction, and the models (including their underlying biological basis) used to derive exposure and risk estimates. Region 8 feels strongly that the document will require extensive revision prior to an external review.

Section 1, Introduction

Page 1-1, Line 33: "cc" is not previously defined and should be.

Pg 1-4 The discussion of the mineralogy of Libby amphibole (LA) is inconsistent with Meeker et. al. 2003. LA is a mixture of winchite, richterite, tremolite, magneiso-riebeckite, magneiso-arfvedsonsite and edenite [84:11:6:<1:<1:<1]. The authors should correct the description of LA in Section 1.2 and then be consistent throughout the entire document with the terminology/description of LA.

Page 1-4, Line 15: Richterite is misspelled.

Page 1-4, Lines 15-16: The document states "These [LA] fibers exhibit a range of morphologies from asbestiform to cleavage fragments (Meeker et al., 2003)." A careful read of Meeker et al. reveals this is not in the spirit of Meeker's conclusions: "There are no distinct morphological boundaries by which to categorize the amphiboles". WeI urge the authors to carefully read the last two paragraphs of Meeker's 2003 article more carefully. Why perpetuate the misconceptions and

confusion about cleavage fragments, when there are more accurate ways to describe the morphology?

Page 1-4, Lines 18-22: What about autoimmune diseases – specifically Noonan's work? And Larson's work showing increased risk of cardiovascular disease?

Page 1-4, Line 25: It would be helpful to provide some characterization of the uncertainties associated with applying the AAHAU IUR to different minerals/environments, rather than simply state there is some uncertainty.

Section 2, Geology, Use and Exposure Potential

Page 2-1, Line 7: Suggest using an alternative to the word "entrained" in this context. As defined by multiple online dictionaries and typically used in the asbestos arena, "entrained" suggests suspension of a solid in a fluid or air stream; to carry along in a current.

Page 2-1, Lines 12-17: What about Noonan's work related to autoimmune disease and Larson's work regarding cardiovascular disease?

Page 2-1, Line 18-19: Lockey 1984 and Rohs 2008 also report interstitial abnormalities in workers exposed to LA. An increase in interstitial changes was noted from 0.2% in 1980 to 2.9% in 2005.

Page 2-1, Lines 19-30: This paragraph makes it sound as if the only way workers were exposed to LA was through popping.

Page 2-1, Lines 27-28: Please include reference for 80% statistic.

Page 2-1, Lines 31-33: This sentence does not seem to belong here. It addresses exfoliation plants in the town of Libby, but the next sentence refers to unexfoliated product being shipped to expansion plants in other areas of the country. Perhaps a transition is needed?

Page 2-2, Figure 2-1: Is a rough estimate of time frame for this photo available?

Page 2-3, Lines 10 and 11: Consider replacing "amphibole asbestos fibers" and "amphibole asbestos fiber containing waste" with "Libby amphibole asbestos fibers" and Libby Amphibole asbestos fiber-containing waste" to be consistent with previous references to the amphibole contamination found in Libby vermiculite (e.g., page 1-1, Lines 3-3; Line 33; page 1-2, Line 1, et al.).

Page 2-3, Line 14: Did a mineralogist write this section? If not, suggest having one review it carefully.

Page 2-3, Lines 18-21: check use of term "fibrous". It is contradictory or misleading to say "the amphibole **fibers include** tremolite asbestos and related **fibers** and the **nonfibrous** magnesioriebeckite amphibole."

Pg 2-3, lines 17-21: The description of the geology of the Rainy Creek complex is inconsistent with published reference materials [Boettcher, 1996, Meeker et. al, 2003, Wylie and Verkouteren, 2000].

Suggest having a geologist draft this section. See above for consistent definition of LA.

Page 2-5, Line 37: Use of terms describing habit, such as "asbestiform", before those terms have been defined, is confusing to the reader. Please consider having this section carefully edited by a mineralogist familiar with Libby Amphibole asbestos.

Pg 2-7 Why don't you show a picture of Libby vermiculite ore, considering this Tox Profile is on LA.

Page 2-7, Line 1: Should "determines" be replaced with "depends on"?

Page 2-7, Table 2-1: Please define what is meant by "perfect" cleavage.

Page 2-8, lines 9-14: This paragraph is a supplication of the last paragraph on Page 2-7, lines 18-23.

Page 2-9, Line 32: Please change "NA" to "Na".

Page 2-9, Line 35: Please insert a space so that "invaried" reads "in varied".

Page 2-11, Line 13: Insert a space between "Leaky" and "et".

Page 2-15, Lines 1-2: Does this sentence imply that "cleavage fragment" is a habit?

Page 2-15, Lines 7-10: The prismatic habit, while mentioned in Line 1 of this page, is not included in this set of definitions. Please clarify.

Page 2-16, Line 2: Should "mines" be "mine"?

Page 2-16, Line 8: Why are cleavage fragments noted? How are cleavage fragments identified?

Page 2-16, line 12: The term "aspect ratio" has not been previously defined.

Page 2-16, Figure 2-11: In the caption, the term "blocky" is introduced, yet not discussed in the text. Please clarify. Also, what is the purpose of referring to "cleavage fragments" in the caption? How is it known that these are "Possible cleavage fragments"? What is the purpose of distinguishing them as such? Consider identifying (i.e., labeling) the different fiber morphologies present in this figure.

Pg 2-17 The initial collection of airborne fibers at Libby was using mini-impingers, then filter cassettes.

Page 2-17, Lines 21-22: Robust fiber size distribution data are available for Libby Amphibole asbestos exposures in the community (collected by EPA), but fiber size distribution data for occupational exposures occurring in and associated with the Libby mine and operations are not available.

Page 2-17, Line 25: The first sentence of this paragraph refers to particles and fibers in air samples. Has the difference between fibers and particles been defined earlier (or anywhere) in this document?

Page 2-17, Line 34: Consider replacing "the material" with "composition" to improve clarity.

Page 2-18, Line 2: The distinction between "fibers" and "asbestos" may not be apparent to the general reader. Consider rewording as "fibers in general or asbestos."

Page 2-18, line 5: In line 5 the term "length-to diameter ratio" is used, but in line 10 the term "aspect ratio is used to describe the same parameter. Please standardize and define all terms used in this report.

Page, 2-18, Lines 12-13: To which NIOSH method does this sentence refer? Certainly not NIOSH 7400 as that is based on PCM. Please clarify.

Page 2-18, Lines 21-23: The wording "This measure" is confusing. Please reword to clarify that "This measure" refers to PCM, not fibers with a lower length cutoff of 0.08 microns (by TEM). Why are PCM measurements expected to be proportional to estimated cancer risks? Please provide justification for this assumption. How can PCM measurements be expected to be proportional to cancer risk if the proportion of PCM fibers depends on mineral type, sampling, and handling? Is the reader to then infer that cancer risk is related to mineral type, and/or sampling and handling procedures? A few extraneous characters ("<", "-") are noted in these lines. Please delete.

Pg 2-19, line 28: Correct reference is U.S.EPA 2008 if one is referring to the Framework.

Page 2-20, Lines 15-23: Please include a description of paraoccupational exposures in this section. This section is incomplete in that it does not address paraoccupational exposures. Please add this to the discussion of lifestyle, activity, lifestage factors that may influence exposure. Additionally, the potential for increase susceptibility due to genetic factors is not mentioned. This should at least be mentioned, as there are examples of familial disease patterns in Libby residents, difficult to sort out whether due to genetic predisposition or increased exposures.

Page 2-20, Line 22: Please change "my" to "may".

Page 2-20, Line 31: Please check capitalization of Libby amphibole asbestos. In earlier sections of the document, the material is referred to as "Libby Amphibole asbestos."

Page 2-21, Line 14: Please insert a period after "insulation" and capitalize "community".

Page 2-21, Lines 23-26: Many, many, many additional samples collected between 2001 and 2008 document the presence of Libby Amphibole asbestos in outdoor and indoor environments (soil, dust, air, tree bark, duff). It is not clear why a 2001 document is referenced when more robust and current data are available.

Page 2-21, Lines 27-28: The sentence states "There are no historical measurements of the levels of amphibole fibers community members may have been exposed to during plant operations." A few ambient air measurements were taken in downtown Libby when the plant was operating.

Page 2-21 (Lines 27-35), 2-22 (Lines 1-21), and 2-23 (Lines 1-16): It is unclear why the extensive indoor and outdoor activity-based sampling effort that took place in 2006 – 2008 is not mentioned in this discussion. Many samples were collected that provide a robust dataset informing community exposures. The report can be found at ftp://ftp.epa.gov/r8/libby/OU4_ABS_Results/

Pg 2-23, Lines 19-22: The discussion of fibers in tree bark and the Ward paper in 2007 are confounding. The initial Ward paper dealt with PM 2.5 emissions and PAHs; not LA fibers. Speculation concerning logger exposures and exposures at schools. We have no data on how to address actual human exposure.

Page 2-23, Lines 23-25: The statement "Additionally, schools in Libby reportedly had high levels of particulate matter due to the use of wood heat during the winter (Ward et al., 2007)" may be misleading to the reading because particulate matter does not equal fiber exposure. Other components of wood smoke can contribute to particulate matter. While it is plausible that burning of contaminated wood may have contributed to residential exposures (see Libby Conceptual Site Model), it is not accurate to equate particulate matter with Libby Amphibole asbestos. Please add a sentence or two to clarify the difference.

Pg 2-23 (Lines 34-35) 2-24 (Lines 1-3): Inclusion of the O M Scott facility in Marysville OH as an exfoliation facility is not entirely correct. They had an exfoliation facility but they did not make vermiculite insulation. Suggest elimination of this example. Of the 105 exfoliation site, none had potential exposures equivalent to Libby.

Pg 2-24 (Line 31) Define PLM.

Page 2-25, Line 17: Ewing 2010 is missing in reference section.

Section 3, Fiber Toxicokinetics

Page 3-1, Line 1: I am heartened to see a discussion of fiber kinetics (retained dose) in this document. However, as it stands, the section is superficial and requires more in depth discussion. Include discussion of aerodynamic diameter versus equivalent diameter. The beginning of this section should include an in-depth discussion of airway anatomy/architecture and relevant physiology, and well as discuss basic concepts in fluid dynamics.

Page 3-1, Figure 3-1: Please consider whether the figure ought to include an arrow from the pleural tissue back to the parenchymal tissue compartment. There should be an arrow from the sputum to the gi tract. Blood is shown as a "dead end" compartment, meaning there is no movement out of the blood compartment. What is the reasoning/evidence for this? Why even show the blood?

Page 3-2, Lines 15-18: For Libby residents, another route of exposure via ingestion includes consumption of game, fish, fruit, and/or vegetables harvested from contaminated areas.

Pg 3-3 Figure 3-2 refers to particles. Are these fibers or particles? Fibers behave very differently than particles.

Page 3-5, Line 12: Diffusion is misspelled. Also, change "The" to "this".

Page 3-5, Line 19: Electrostatic is misspelled. Change predominant to "predominate".

Page 3-4, Table 3-1: Why cite a 1986 version of C& D, when more current information is available?
Page 3-5, Line 33: A word appears to be missing from the phrase "...and would be used to XXX depositional patterns...".

Page 3-5 and 3-6: The discussion in this section is superficial. The difference between aerodynamic diameter versus fiber equivalent diameter should be considered. What is meant by "the shape factor often approaches 1"? "d_g" is not defined. Is an aspect ratio of 3:1 considered high?

Page 3-6, Lines 2-7: The sentence beginning with "Translocation of fibers..." appears twice.

Page 3-6, Line 3: Delete the word "be".

Page 3-6, Line 9: Has the term "matrices" been defined?

Page 3-6, Line 13-14: Another important point to be made here is that oronasal breathing, especially under conditions of exertion, can increase turbulence in airways and can impact deposition.

Page 3-6, Lines 21-23: Aren't there more articles than this?

Page 3-6, Line 28: It is unclear why Table 2-2 is referenced at the end of a statement addressing physical criteria necessary for deposition into the deeper regions of the respiratory tract. Table 2-2 does not provide physical criteria of Libby Amphibole asbestos fibers, but does refer to the concentrations PCM, PCMe air sampling results. Please clarify.

Page 3-6, Line 32: Change "length" to "lengths".

Page 3-7, Line 12: Change "effect" to "affect".

Page 3-7, Lines 7-12: Also the uterus (provide citations).

Pg 3-7 LA fibers are known to "clump" in biological systems which complicates not only deposition but clearance. Pulmonary surfactants and macrophages also tend to "clump" fibers.

Page 3-8, Lines 21-23: These two sentences seem out of place here. Mechanical forces pressure differentials associated with inspiration/expiration might be more predominant in the intrathoracic spaces rather than the upper respiratory region where pressure equalization is more likely, and where excursions of chest wall associated with inhalation and exhalation are more pronounced (not so much in the tracheal region).

Page 3-8, Lines 29-30: This sentence states that once ingested, fibers may adversely affect the tissue, or enter the body. Yet previously, the importance of ingestion of fibers is downplayed.

Page 3-9, Line 18: Smaller fibers can also be "removed" by other processes, e.g., translocation to other tissues.

Page 3-9, Line 21: Provide the reader with an idea of size range associated with alveolar macrophage engulfment.

Page 3-10, Line 1: Provide the reader with an idea of size range that is too large to be engulfed by alveolar macrophages.

Page 3-10, Lines 3-4: Suggest removing this sentence (beginning with "Although unknown"), as speculative statements don't belong in an IRIS file. Alternatively, if retained, change "unknown" to "unproven". Also, consider the level of speculation associated with this statement, and the lack of including other unproven or speculative, or postulated, information elsewhere in the document. The comparison seems incongruent, in that in this instance, speculation is included, but the remainder of the document does a very incomplete job of providing the reader with postulated, unproven, or speculative information.

Page 3-10, Lines 13-14: The sentence "The presence of iron in the coating, however, could provide a source for catalysis of reactive oxygen species similar to that observed with fibers" does not support the assumption that this section is addressing, which is that encapsulation of fibers is a clearance mechanism.

Pages 3-10 (Lines 29-35) and 3-11 (1-5): It is not clear how this section is related to the discussion of translocation to extrapulmonary tissues. Somehow this section has morphed into a discussion of fiber size distributions in different tissues. While this is a useful and important discussion, it is not clear how it fits into this section. A stand alone section for this topic would be more useful, with the goal of the discussion clearly outlined at the beginning of the section (i.e., does mineralogy and/or morphology affect translocation to extrapulmonary tissues). There are many other studies that should be included in this discussion.

Page 3-11, Lines 6-30: See comment above. What started out as a discussion of clearance mechanisms has become an attempt to distinguish the influence of fiber dimension and/or mineralogy on translocation to other tissues. Suggest considering whether or not this information is critical to the document, and if so, demarcating this section as a standalone section, and presenting a complete review of the literature.

Page 3-11 (Lines 31-34) and 3-12 (Lines 1-2): This paragraph seems to capture the goal of the previous paragraphs, and should be considered for the opening lines of a discussion of fiber dimension and/or mineralogy with respect to tissue translocation.

Page 3-12, Line 5: Delete the comma after "infants".

Page 3-12, Line 14: It is not clear why the discussion in the previous section regarding translocation to extrapulmonary sites is not instead part of this section, as opposed to the previous section entitled "Respiratory Tract". Document organization is poor.

Page 3-12, Lines 24-33: This is a poorly written summary. Is the text truly meant to conclude that absence of histopathological changes is evidence of lack of translocation? Were fiber burdens evaluated? In what tissues? As written, this section does not adequately address clearance from the gastrointestinal tract.

Pages 3-12 (Lines 33-34) and 3-13 (Line 1): No evidence is provided to support the observation the no translocation occurred. How was translocation evaluated? Fiber burden? No details are provided; as such, this section cannot be evaluated.

Page 3-13, Lines 9-21: The material presented above in Section 3 does not support the statement that inhalation is the main route of human exposure to asbestos. Fiber deposition in the respiratory tract is in fact poorly defined, since most of the references cited/available relate to particle, not fiber deposition. As written, this is not worth including in the document. Dissolution is not a biological mechanism. "These mechanisms rely heavily on fiber characteristics" is unsubstantiated. Which characteristics? How specifically do they influence deposition and clearance? Literature citations provided in this section are meager.

Section 4, Hazard Identification of Libby Amphibole Asbestos

Pg 4-2, Lines 1-2: The Whitehouse study [2008] reports 4 additional mesothelioma cases in miners from Libby. Based in Sullivan et. al. 2007, Larsen, et. al. 2010 and Whitehouse et. al. 2008, there appears to be perhaps 19 cases of mesothelioma reported in miners from Libby.

Page 4-2, Lines 13-14: The statement that "No occupational studies are available for exposure to tremolite, richterite or winchite mineral fibers as a mixture or as single exposures." This is incorrect. Miners in and around Libby and workers at the Marysville, OH O M Scott plant have been exposed. Workers at the approximately 105 daughter sites have also been exposed to Libby amphibole.

Page 4-2, Lines 15-19: The exposures from whitewash in Turkey (Cappadocia) are primarily to erionite, a zeolite; not tremolite.

Page 4-2, Line 22: Anthophyllite is misspelled.

Pg 4-3 Discussion of published reports on Libby miner cohort should include Whitehouse et. al. 2008.

Pg 4-3, Lines 20-23: Please provide references to ore handling practices cited in the text. Were the bagging and exhaust stacks changed in 1974? Source of information?

Pg 4-4, Line 21: The abbreviation of million fibers per cubic foot [mppcf] should be listed in the acronym section early in the document.

Pg 4-5 In Table 4-1, the Marysville, Ohio worker cohort is introduced. The focus of the Marysville study was on pleural disease; not lung cancer and mesothelioma. Since this document pertains to the carcinogenicity of Libby Asbestos, is it really appropriate for this information to be shown in Table 4-1? Incidentally, the dates of Libby ore use at Marysville are incorrect.

Page 4-6, Table 4-2: Footnote 3 is missing.

Page 4-6, Line 24: Is "LO" previous defined? If not, please define. Consider including in list of acronyms at beginning of document.

Page 4-6, Line 24: Amend beginning of sentence as follows: "For exposures occurring prior to 1968,...".

Pg 4-7 The job exposure matrix developed for the miner cohort is not provided. It should be included as an appendix to the document. The summary of the JEM is presented in Table 5-2. It appears that the JEM covered exposure dates from 1959 to 1982. There is no mention about worker habits such as the number of smokers in the cohort/JEM.

Page 4-8, Line 23: Change "researches" to "researchers".

Page 4-9, Lines 7-10: This section does not acknowledge the limitations associated with a length cutoff of 4.98 microns in these analyses (fibers shorter than 4.98 microns were not included in the evaluation). This is important because roughly 45% of the fiber size distribution in Libby environmental samples falls below 5 microns in length.

Pg 4-9 Table 4-3 and text are inconsistent. Fiber width >2.49 not 1.76.

Page 4-11, Table 4-4: Add "Sullivan" to the first cell of the table in the column "Reference(s)". In the second cell in the same column, add ")" after "Larson et al. (2010b".

Pg 4-11, Table 4-4: Suggest that the Whitehouse [2008] paper be referenced her and include the 4 additional miners diagnosed with mesothelioma. Page 4-12 states that mesothelioma data was based on data from 1999 to 2001. This under-reports the number of meso cases and, as used later, under estimates meso potency in the model.

Page 4-12, Line 12: Delete "was".

Pg 4-15, Lines 24-25: Larsen adjusted relative risk due to smoking using a bias-adjustment factor of 1.3. Was this carried over to the modeling?

Pg 4-16, Line 17: Larsen [2010]report 19 miner mesotheliomas in 2010. Whitehouse et. al. 2008 reported 4 additional miner mesotheliomas. Reporting of numbers of mesotheliomas appears to be inconsistent and perhaps under-reporting of the disease.

Page 4-18, Table 4-5: Insert "Sullivan (2007)" into lower left cell under the column "Reference(s)".

Page 4-27, Table 4-8: Add Noonan citations to cells in left-hand column under the heading "References".

Pg 4-30 to 33: As mentioned previously, the discussion of the Marysville, OH plant appears to be out of place. The focus of this Toxicological Review is the carcinogenicity of Libby asbestos, not the non-cancer effects observed in the Marysville, Ohio cohort. History is incorrect while the data seem adequately reported.

Pg 4-65, Line 20: chromosomal aberrations; not number.

Pg 4-75, Lines 20, 21: Add Whitehouse 2004 and 2008.

Section 5, Exposure Response Assessment

Pg 5-1, Lines 17-19: This document should provide not only an IUR for continuous lifetime exposure, but also IUR values for a range of alternative age at first exposures and durations of exposure. The subsequent recommendation to evaluate less than lifetime exposures using a prorated IUR does not seem wise.

Page 5-2, Lines 5-6: How will Section 2 (retained dose, i.e., deposition and clearance in respiratory tract) be integrated with the exposure-response modeling?

Page 5-2, Lines 8-11: This is likely because a different mode of action (including target tissue dose) is in play for lung cancer versus mesothelioma.

Page 5-2, Line 13: The document should provide rationale for the choice of 1% as extra cancer mortality risk.

Page 5-2, Line 21: For the sake of congruency, explain why an absolute risk model is used for mesothelioma (rarity in general population) and insert example of absolute risk equation.

Pg 5-3, Lines 18-19: Please provide an explanation as to why observations of the current population of Libby are not used (e.g., no quantitative exposure data)

Page 5-5, Line 16: Provide justification for choice of these two types of cancer as endpoints of concern (asbestos is known to cause other types of cancer, e.g., laryngeal, digestive tract, ovary likely not applicable due to small number of female cohort members).

Page 5-7, Line 3: Move "(Figure 5-1)" and insert directly after "Sullivan (2007)", in order to improve clarity regarding what exactly Figure 5-1 represents. As written, the text implies that Figure 5-1 represents the Amandus and Wheeler (1987) JEM.

Page 5-8: Please provides units for the exposure intensities shown in Table 5-2.

Pg 5-10 The estimation of exposure in the dry mill from 1956 to 1969 was by midget impingers which measure total dust. The asbestos fiber counts were only estimates with significant uncertainty. Also there were extrapolations from pre-1967 exposures based on post-1967 measurements and worker recall in 1982. These assumptions were used to develop exposure data for the IUR while

similar exposure data supporting the development of the reference concentration were discounted by NCEA. It appears that exposures were extrapolated to and 8 hour TWA for 365 days per year. This would tend to overestimate the actual worker exposure since most workers only worked 5 days per week.

Pg 5-11, Table 5-3: Delete comma in year. The sub-cohort of 880 workers was used to develop JEM for exposure assessment. The uncertainty in exposure estimation prior to 1960 is warranted.

Page 5-11, Lines 24-27: As written, the text is very unclear as to what exactly Figure 5-1 represents. Sullivan 2007? Or additional job assignments and/or all workers regardless of race or gender?

Page 5-12, Lines 13-17: Please clarify the use of the term "greater" in the first sentence to describe uncertainty associated with assumptions used to estimate exposure intensity in early decades. The range of conversion factors derived by Amandus and Wheeler is 1,2-11.5 fibers/cc per mppcf. The chosen conversion factor of 4.0 fiber/cc per mppcf is 3.3 times greater than the low end of the range and 2.9 times less than the high end of the range. The example provided in the text states that exposure intensity may vary as much as 3-fold between the high and low estimates. This range of uncertainty seems about the same as (not greater than) the range of uncertainty associated with the chosen conversion factor.

Page 5-13, Figure 5-2: Axis labels are difficult to read.

Pg 5-14, Lines 12-14: As written, CE has units of f-days/cc. The traditional units is f-yrs/cc. Clarify the units of CE, perhaps by dividing by 365 days/yr.

Page 5-14, Lines 22-30: The justification for use of RTW provided in the text assumes that much is known about the influence of fiber kinetics on tissue damage and development of disease. While residence time is an important consideration with respect to choice of exposure metric, additional information is needed to support the underlying assumptions, or refine them as necessary based on more accurate information regarding fiber kinetics. For instance, the sentence "Similarly, fibers that translocate to the pleura may damage cells as long as they remain in this tissue" (Lines 27-28) assumes that the fiber must be continually present to cause damage. It is not known whether the fiber must be continually present to cause damage, or whether transient presence is all that is required to initiate a cascade of events leading to damage. Also, RTW should be based on knowledge of target tissue concentrations, not external airborne exposure concentrations.

Page 5-15, Lines 18-26: The discussion in this paragraph is based on the assumptions that 1) the fiber must be continuously present in a tissue to cause damage, and 2) clearance of a fiber from a tissue is associated with less damage. These assumptions are not grounded in knowledge of fiber kinetics or how fibers initiate damage in target tissues, or how the damage is sustained. For example, repair mechanisms can and do occur even when the fiber is present in the tissue (in other words, the fiber does not have to leave the tissue in order for repair to take place). Also, as stated in my preceding comment, do we know that the fiber must be continually present in order to cause damage? It is entirely plausible that fibers can initiate a cascade of events that continues even after they have translocated to another tissue.

Page 5-16, Lines 30-32: Are the chosen half lives physiologically relevant with respect to fiber kinetics in lung and pleura? If not, the relevance of their use in these models is questionable.

Pg 5-18, Line 10: The analysis was based on work history from 1960 to 1982 (22 years). Lagging exposures by 10, 15, and 20 years reduces exposure analysis from 12 to 7 to 2 years. What is the justification for this?

Pg 5-18, Section 5.4.3.1: This key section is not at all clear. What model is being fit to the meso data? What is the equation? The exposure-response model must have a cubic time term in the equation as a time metric. We were expecting an equation that gives incidence (risk) of meso at some specified point in time (age), calculated as a function of the exposure metric, and also some time metric (similar to the Q term in the IRIS model) that is related to time since exposure.

The Poisson equation, as written, does not have any terms that are related to exposure or latency. Also, aren't the data fit at the individual level? If so, isn't the probability model binomial, not Poisson?
This text needs work to clarify what was done, and why.

Page 5-18, Lines 26-32: An alternative to empirical modeling is the use of defined deposition and clearance models (to define target tissue dose) in concert with knowledge of mode of action to derive a model based on greater understanding of underlying biology and toxicology of fibers.

Page 5-19, Line 9: Equation 5-6 is missing.

Page 5-19, Line 11: A variable used in Equation 5-6 is missing.

Page 5-20, Line 3-14: Results from all model evaluations should be provided in the interest of transparency.

Page 5-20, Line 17: It is unclear why the evaluation of the full Libby worker cohort (n=1871) is included in this section when a previous section defined the cohort for this evaluation as those workers hired post 1959 (n=880).

Pg 5-21, Lines 7-8: What is this sentence implying? Do you mean that you fit the IRIS model and it had a poor DIC, or that you tested C*Q as an exposure metric in some other model?

Pg 5-22, Line 25: What does the superscript T represent in Eq. 5-7?

Pg 5-22, Lines 28-31: Yes, but it sweeps upward at high dose. What evidence exists to support a non-linear relationship? Previous EPA fitting assumed linearity at all exposures. Have you compared a linear model with the Cox PH model?

Pg 5-24: The cutoff date for patient follow up appears to be December 31, 2006. This excludes data from Larsen et. al. 2010 and Whitehouse et. al 2008. Larsen et. al. 2010 reports 19 cases of mesothelioma in the miner cohort. This is more than double the reported n=7 used in the modeling. The increased incidence should have a significant effect on the model results and the mesothelioma

contribution to the IUR.

Page 5-25, Lines 8-10: The models for mesothelioma and lung cancer yield puzzling results that are explained by a consideration of sources of uncertainty with respect to exposure estimates, life-stage, and life-style factors; in fact, the discussion in Lines 12-41 on Page 5-25, continued on Page 5-26, Lines 1-19, does a good job of considering the sources of those uncertainties. Has anyone considered the contribution of uncertainty associated with use of a truncated estimation of fiber concentration (e.g., PCM measurements)? Could the puzzling results discussed here be attributable to uncertainty in exposure estimates that do not consider the entire fiber size distribution? Or an alternate exposure metric such as surface area?

Page 5-26, Lines 2-3: Please include a discussion of ways in which older workers differ from younger workers that could alter responses to exposure. Also, add an "s" on the end of worker to make it plural.

Page 5-27, Line 18: We question whether 7 mesothelioma deaths are sufficient to provide robust analysis and comparisons? Larsen et. al. 2010 reported 19 mesotheliomas in the miner population. The use of 7 cases in the current analysis is low and may provide unreliable modeling estimates.

Page 5-28, Lines 16-18: It is unclear what the underlying biological rationale is for the use of 10 or 15 year lag in exposure and a 5 year half life. Do we know what half lives of fibers in pleural tissues might be? Did you do any plotting of observed vs expected, or is choice of best metric based strictly on DIC?

Page 5-29, Line 12: Delete the "s" from "exposures".

Pg 5-30, Lines 17-23: The logic for using exposure estimates between 1956 to 1967 where total dust measurements [using mini-impingers] provided a basis to estimate fiber concentrations is based on greater uncertainty than the University of Cincinnati exposure reconstruction for the Marysville, Ohio OM Scott cohort for years 1959 to 1972. NCEA complained that these data were "too uncertain" to use for the RfC derivation. Why is this extrapolation procedure acceptable for the IUT and not for the RfC? The midget impinge data used to convert dust measurements to PCM fiber concentrations are highly uncertain.

How does restricting the size of the sub-cohort limit potential confounding due to smoking influences on the rate of lung cancer and mesothelioma? There is no information on smoking in the cohort. Hence the analysis of the lung cancer incidence is severely compromised.

Pg 5-32 In addition to calculating the AIC, were any of the data plotted to estimate goodness of fit?

Pg 5-33 We assume this is conceptually similar to the KL term from previous EPA fitting? If so, maybe calling it potency factor rather than slope would be helpful. Also, it would be helpful to compare this value to the KL presently used by EPA (1E-02 for workplace exposure, 2.8E-02 for continuous exposure).

Pg 5-34, Table 5-7 The topic of extrapolation from workers to continuous exposure requires more explanation and discussion than just a footnote. The extended Cox proportional model estimated a slope based on a 365 day/year exposure. The miner exposures were more adequately described as a 250 day/year exposure. Extrapolation from 250 days/year to 365 days per year requires some explanation. Foot note for Table 5-7 is a beginning. Source of 240 days versus 250 days?

Also, it is undesirable to make the adjustment in 2 steps, separated at different places in the document. As written, an adjustment of 365/240 is made here, and a second adjustment of 20 m3 / 10 m3 is made later.

Recommend creating a stand-alone section to discuss and apply these adjustments.

Page 5-35, Line 1: Add an "s" at the end of "period".

Page 5-36, Lines 2-5: Do these results make sense from a physiological/toxicological perspective? Do we know what half lives of fibers in lung tissue might be?

Page 5-36 (Lines 33-35) and 5-37 (Lines 1-9): Please show results for this sensitivity analysis.

Pg 5-36 You give the slope factor (potency factor ?) results for lung cancer here, but in the preceding section on meso, you only discuss which exposure metric is best and do not give the slope factor values. Recommend that you add info on the best fit parameters and CIs in the meso section, analogous to the section on lung cancer

Pg 5-37 See previous note pg 5-34. Recommend creating a stand-alone section on extrapolation from worker to continuous exposure that has all adjustments presented in the same place.

Page 5-38, Lines 24-28: The extrapolation from occupational exposure to continuous environmental exposures should be more clearly presented.

Pg 5-38 Why not use an IUR for partial lifetime extrapolations? This would seem to be more logical than linear proration. See Framework, 2008. Why not include older ages since the 70 year period underestimates
lifespan.

Pg 5-39 This approach seems very strange.

First, the IUR is supposed to give the risk of death from asbestos before death from something else. Choosing 70 years as "lifetime" does a serious disservice to people who live longer than 70 years. Second, even if you want to stick with a standard exposure scenario of 0-70 years, why calculate the risk from 16 to 70, and then perform a linear extrapolation. Do you believe that exposures from age 0-15 are equally likely to cause death as exposures from 16-30? I think the available evidence shows that early exposures are more hazardous, especially for mesothelioma. Recall that for Libby, this is a closed community and people live here longer than 70 years [at the same place].

Pg 5-39 This does not seem right. Risk from a 10 year exposure from age 0-10 should yield a higher

risk than a 10-year exposure from age 40-50. Simple proration does not account for this. Why not calculate IURs for a range of alternative scenarios (age at first exposure, exposure duration) rather than recommending proration as if IUR were a constant.

Pg 5-40 0.01/0.313 = 0.032 not 0.025
0.032*70/54 = 0.041 not 0.032
Seems like there is a factor of 54/70 going on here

Check and correct calcs as needed

Pg 5-40, Line 33: We recommend using the published data rather than adjusting for under reporting mesotheliomas by using the statistical method of Kopylev et al 2011. This statistical method yields a estimate of 10 [9.7] predicted cases. 10 is still 9 less than the 19 reported by Larsen et. al. 2010. Use of the lower value, under estimates theoretical potency of LA for inducing mesothelioma.

Page 5-41, Table 5-10: It is unclear why decay half time of 5 years was used in the mesothelioma analysis and no decay half time was used in the lung cancer analysis.

Pg 5-42 The authors refer to Appendix B for estimation of lung cancer-specific extra risk while accounting for competing causes of mortality. Appendix B might mean something to a person who understands the models used to derive these values; however, a lay person who might be casually interested in how the estimates were derived would be completely lost.

This document should provide not only an IUR for continuous lifetime exposure, but also IUR values for a range of alternative age at first exposures and durations of exposure. Following the later alternative, the life table calculations would require re calculation.

Pg 5-43 Risk is computed out to age 85 based on 22 years of exposure data. Even if risk were estimated out to 70 years, one is still extrapolating out over the actual exposure data used for the model. NECA balked at extrapolation from 47.5 year of exposure data to a 70 year life time for a lifetime RfC derivation. Is this a double standard?

Page 5-46, Line 14: The rationale and methodology for derivation of an IUR for mesothelioma and lung cancer combined are not clearly described. The IUR for combined disease is not based on the uncertainty around the sum of the two best estimate values, but is an upper bound on the sum of the highest individual values? This seems like compounding conservatism to me. Why not use Monte Carlo to generate alternative values for each and get the distribution of IURs from the life table?

Pg 5-48 Table 5-14 At the end of the data, the risk estimates do not seem plausible [or believable]. The IRIS value for combined lung cancer + meso for continuous lifetime exposure is 0.23. Based on the new approach, here is what this reviewer expected:

1) Based on using 2007 rather than 1970 mortality statistics, the new value should go up.
2) Based on using data for amphibole only rather than a mixture of amphibole and chrysotile, the number should go up, especially for meso [especially since meso drove the 1988 IUR; weighted by amphiboles].

3) Based on presenting an upper bound rather than a best estimate, the number should go up.

However, the value is lower. At a minimum, the text needs a discussion to compare and contrast the new value to the old value, and discuss why it is different.

Pg 5- 49 Exposure from age 25 to 55 would yield the same risk. This does not seem appropriate.

Pg 5-49 This reviewer recommends that NCEA consider re-evaluating the mesothelioma data and the modeling of the data to yield a unit risk term. The modeling does not contain a time term and the number of reported mesothelioma cases [n=7] is so low that there is virtually no statistical power using the data. The published literature [Larsen et. al. 2010 and Whitehouse et. al. 2008] indicate more than double the number of mesothelioma cases for members of the miner cohort. NCEA could argue that the additional cases were reported after the December 31, 2006 cut off time; however, both reported investigations covered reporting prior to the 2006 cutoff. NCEA should consider using the Larsen et. al. 2010 data to support the mesothelioma portion of the IUR estimation as a scientifically prudent and justifiable position.

Page 5-49, Lines 18-25: These equations and examples are poorly (unclearly) illustrated. Suggest writing equations in mathematical format rather than in a continuous line of text.

Page 5-53, Lines 14-33: This section acknowledges a major source of uncertainty associated with the exposure assessment. A follow-on uncertainty that is not discussed is that which is associated with lack of knowledge regarding the role of the particles not included in the PCM counts with respect to target organ dose and toxicity. At one point, TEM evaluation of archived slides representing historical exposures at the Libby mine was being considered. Such an analysis has been performed for other asbestos-exposed populations and would provide greater insight into the department-specific complete fiber size distributions.

Page 5-58, Line 22 (Uncertainty in statistical modeling section): I appreciate the inclusion of this section in the uncertainty analysis; however, in the interest of transparency, model results should have been more explicitly included.

Page 5-62, Line 7 (Uncertainty in selection of exposure metric section): The choice of values for half lives and decay rates is highly uncertain, and not based on knowledge of underlying physiological processes governing retained dose (deposition and clearance).

Section 6, Major Conclusions

Pg 6-1 There was only one [1] Libby mine. The statistic should be consistent with what has been previously reported in Section 2.

Pg 6-2 The discussion of other exfoliation sites in the US should be consistent with Section 2. Discussion of the Western Mineral Plant is new and not previously reported in Section 2. Reference to the O M Scott plant adds nothing to the discussion unless it Is used to note that pleural diseases

were noted at this facility.

Pg 6-7 The authors again discuss the modeled decay rate ranging from 5 to 20 years. No rational is provided for choosing a decay rate of 5 years for mesothelioma and 0 for lung cancer.

Pg 6-9 The arithmetic for lifetime central estimate values is calculated by this reviewer as 0.041; not 0.032 per fiber/cc. See similar comment in Section 5. This reviewer suggests that the unit risk value[s] for mesothelioma are significantly underestimated based on literature reported data and modeling inconsistencies.

Pg 6-13 Table 6-1 should be revised pending re-evaluation of the mesothelioma reported data and the modeling considerations.

Pg 6-14 This document should provide not only an IUR for continuous lifetime exposure, but also IUR values for a range of alternative age at first exposures and durations of exposure. The IUR should be consistent with the current U.S. EPA Framework Guidance [2008]. The subsequent recommendation to evaluate less than lifetime exposures using a prorated IUR does not seem wise.

Missing references

Ewing et. al. 2010

Lowers and Bern, 2009

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21 March 2011

MEMORANDUM

SUBJECT: Comments on Draft Charge Questions for the Toxicological Review Libby Amphibole Asbestos

FROM: Susan Griffin, PhD DABT, David Berry PhD, Wendy O'Brien, PhD and Robert Benson PhD
Region 8 Toxicologists

TO: Karen Hammerstrom, PhD
IRIS Program

The charge questions do a good job of addressing the general issues surrounding the derivation of the IUR for Libby Amphibole Asbestos. However, Region 8 would like to focus the attention of the external reviewers on specific information and specific issues to include in their deliberations. In addition to the charge questions listed we would like to see the following questions addressed:

1. The ongoing occupational cohort study of vermiculite miners and millers exposed to Libby Amphibole asbestos (Sullivan, 2007) was selected as the basis for the derivation of the IUR. Region 8 is concerned that this under reports the number of mesothelioma cases and underestimates mesothelioma potency in the model. The Whitehouse (2008) paper included four additional miners diagnosed with mesothelioma. The Larsen (2010) paper reported 19 miner mesotheliomas in 2010. Please ask the external reviewers to **specifically** consider the Whitehouse and Larsen data and provide recommendations for either including or excluding the subjects from the Libby sub cohort.

2. Please ask the reviewers to comment on the use of simulated decay models in the determination of exposure metric for both the mesothelioma and lung cancer models. Has this approach been appropriately conducted? Are there other approaches that should be considered?

3. The analysis of the Libby sub cohort was based on a work history from 1960 to 1982 (22 years). If the exposure is lagged by 10, 15, or 20 years, this reduces exposure analysis from 12 to 7 to 2 years. Please ask the reviewers to comment on the appropriateness of this approach.

4. The best fitting model for mesothelioma exposure response was selected for derivation of the IUR. For the exposure response modeling for lung cancer, the best fitting model was not used. Instead a model which assumed no decay half time (which doesn't seem biologically plausible) was used to derive the IUR for lung cancer. The IUR derivation based on combined mesothelioma and lung cancer mortality discarded the individual models selected and used upper bound estimates on the sum of the highest individual values. The current external reviewer questions ask if the exposure-response modeling and determination of the PODs from lifetable analysis been appropriately conducted and clearly described. Region 8 would like the reviewers to specifically provide input and recommendations on the **selection** of exposure response models used in the derivation of IURs for mesothelioma and/or lung cancer mortality.